REMARKS

I. Status of the Claims

Claims 26 and 30-53 are pending in the application, claims 1-25 and 27-29 having been previously canceled. Applicants thank the examiner for withdrawing the previous alleged lack of enablement rejection under 35 U.S.C. §112, first paragraph. Claims 26 and 51-53 are under examination and are rejected under 35 U.S.C. §.S.C. §103 over a new obviousness rejection based on Dorken *et al.* in view of Lee *et al.* and Kaisheva *et al.* The specific grounds for rejection and applicants' response thereto, are set out in detail below.

Claims 30-50 are presently withdrawn, and withdrawn claims 30 and 46 have been amended in the amendment above to depend from claim 26; claim 45 is canceled. Should the present response result in the allowance of composition claims 26 and 51-53, Applicants request reconsideration of rejoinder of the withdrawn claims that now depend from independent Claim 26.

II. Rejection Under 35 U.S.C. §103

Claims 26 and 51-53 are rejected as allegedly obvious over Dorken *et al.*, U.S. Patent 7,112,324 ("Dorken") in view of Lee *et al.*, U.S. Patent 5,917,021 ("Lee") and Kaisheva *et al.*, U.S. Patent Application 2003/0138417 ("Kaisheva"). Once again, Applicants traverse. The examiner continues to argue that Dorken provides for "single-chain multifunctional polypeptides comprising at least two binding sites specific for the CD19 and CD3 antigen" while admitting that Dorken is silent with regards to the percentage of multimeric form versus monomeric form of the single-chain multifunctional polypeptides and does not teach a citrate/lysine buffer with a pH of 6.0-7.5.

The examiner now combines Lee with Dorken, the former allegedly disclosing reagents to attain "biological consistency and stability ... of a monomeric, single-chain antigen-binding protein composition." More specifically, the examiner states that "Lee discloses the addition of amino acids such as lysine [to] help stabilize and protect compositions from decomposition." More generally, Lee discloses stabilized protein compositions comprising a monomeric protein in a composition of sucrose, histidine or glycine, with the Examples providing results from the stabilization of single-chain antigen-binding proteins. However, Applicants submit that a review of Lee discloses the actual discussion of lysine ***in only two locations***. First, in the "Background of the Invention," Lee describes a disclosure in an abstract of Japanese Patent Application 57-26587 of the stabilization of ascorbic acid oxidase by addition of one or more of arginine, lysine, histidine and borates (*see* Lee, Col. 3, lines 12-15). This Japanese document does not disclose the stabilization of single-chain antigen-binding proteins, but rather discloses the alleged stabilization of an enzyme which is a very different protein than a single-chain antigen-binding protein.

Further, and more importantly, Example 3, which is disclosed in col. 10 of Lee, describes an experiment that tests a single-chain antigen-binding protein, CC49/218 sF_v, supplemented with one additive from a list of reagents that includes lysine in a PBS buffer at pH 7.3. The results show that the addition of lysine failed to stabilize the monomeric protein composition against significant aggregation of the molecules after repeated freeze/thaw cycles. The aggregation was measured by a gel filtration chromatography column and the results showed that aggregation exceeded 30% of the monomeric composition, which was an unacceptable result.

Applicants submit that these results showing high levels of aggregates actually teach ***away*** from using lysine in a buffer containing single-chain antigen-binding protein compositions,

and thus against combining the disclosure of Lee (for the purpose of reducing aggregation) with Dorken to arrive at the presently claimed composition.

The Examiner also combines Kaisheva with Dorken and Lee as teaching methods of influencing the dimer to monomer transition of an antibody single-chain Fv fragment, and as specifically disclosing citrate buffer as a preferred buffer to keep the pH in the range of 6.0-6.5. Applicants note that examples of buffers are provided on page 2, paragraph [0021] of the reference. Kaisheva's invention is directed to stable liquid pharmaceutical formulations for immunoglobulin G antibodies. Although citrate buffer is listed as an example of a buffer useful in Kaisheva's claimed pharmaceutical formulations, it is disclosed as being a less preferred buffer because "it causes a painful reaction when injected subcutaneously" (*see* page 5, the 3rd to the last sentence of paragraph [0050] and Example 2, paragraph [0062]). Thus, Applicants submit that one skilled in the art likely would not choose to utilize citrate buffer in a pharmaceutical formulation due to potential subcutaneous administration of the antibody.

Therefore, supported by the above arguments, Applicants traverse the present obviousness rejection based on the examiner's improper combination of Dorken in view of Lee allegedly disclosing single-chain antibodies in a lysine buffer, and Kaisheva allegedly disclosing IgG antibodies in a citrate buffer, where both of these secondary references are considered by the Examiner to have a pH range falling within the claimed pH range. Applicants request that the Examiner reconsider this rejection in view of the arguments provided above that both Lee and Kaisheva teach away from combining their disclosures with Dorken. Applicants submit that it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Applicants further submit that they have provided persuasive arguments that these secondary references should not be combined with Dorken. In view of these arguments, Applicants request that the examiner reconsider his statements that he has made on page 5 of the Final Office Action. Particularly, Applicants request reconsideration of the statement that "it has been well established that the addition of amino acids, such as lysine, are used to stabilize antibody compositions." Lee states that single-chain antibodies mixed with a lysine buffer result in up to 30% aggregation of monomeric antibody molecules which is not the desired result of Lee's invention. Similarly, Kaisheva does not specifically recommend the use of citrate buffer in antibody formulations for certain uses and he ranks citrate as a less desirable buffer than the other buffers disclosed.

Applicants submit that the examiner has not established a *prima facie* case of obviousness as the prior art admittedly fails to teach each element of the claimed invention. Moreover, the claims recite the presence of both citrate buffer and lysine. In view of these arguments, it is requested that the examiner reconsider the declaration of Dr. Thomas Urbig filed with the previous response in February 2011 that provided evidence of surprising and unexpected results for the claimed invention.

To reiterate, and based on these data, Dr. Urbig opines that a composition containing Construct 1 in combination with a buffer comprising citrate and lysine possesses improved stability of the monomeric form of Construct 1 over time, which is an unexpected result as compared with known buffers and other amino acids tested. Thus, even if a *prima facie* case of obviousness had been made out, these data would effectively rebut it.

Reconsideration and withdrawal of the rejection, based on the preceding comments and previously submitted declaration, is therefore respectfully requested.

III. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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